REMARKS

Reconsideration and withdrawal of the rejections of the application respectfully requested in view of the amendments, remarks and enclosures herewith, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 84-118 are pending in this application.

Applicants thank the Examiner for withdrawing the rejection under 35 U.S.C. § 103 based on the Cox reference. Applicants also thank the Examiner for withdrawing the provisional double patenting rejection of claims 84-118 of the instant application as allegedly being obvious variations of claims in co-pending application 09/766,422.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. THE DOUBLE-PATENTING REJECTIONS ARE OVERCOME

Claims 84, 85, 96 and 116-118 remain rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 ("the '473 patent") in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999). Claims 84-91 remain rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733). Claims 84, 92, 94, 95, 100 and 108 remain rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Li (WO 96/40945). Claims 84, 93, 97, 98 and 104 remain rejected under the judicially created doctrine of obviousness-type double patenting as

allegedly being unpatentable over claims 5-8 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Choi et al. (Virology 1998, 250:230-240). Claims 84-118 remain rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), Baker et al. (US Patent 5,106,733), Li (WO 96/40945) and Choi et al. (Virology 1998, 250:230-240).

Claims 84, 85, 96 and 116-118 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of U.S. Patent No. 6,586,409 B1 ("the '409 patent"). Claims 84-91 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of the '409 patent and further in view of Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733). Claims 84, 92, 94, 95, 100 and 108 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of the '409 patent and further in view of Li (WO 96/40945). Claims 84, 93, 97, 98 and 104 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of the '409 patent and further in view of Choi et al. (Virology 1998, 250:230-240). Claims 84-118 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of the '409 patent and further in view of Xiang et al. (Immunity 1995, 2:129-135), Baker et al. (US Patent 5,106,733), Li (WO 96/40945) and Choi et al. (Virology 1998, 250:230-240).

Claims 84, 85, 96 and 116-118 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of the '409 patent. Claims 84-91 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of the '409 patent and further in view of Xiang et al. (Immunity 1995, 2:129-135) and Baker et al. (US Patent 5,106,733).

These rejections are addressed collectively and are respectfully traversed.

There is no teaching or suggestion in the '473 patent to combine a DNA vaccine with a cationic lipid containing a quaternary ammonium salt and having the indicated formula. Furthermore, the Office Action admits that the '473 patent does not teach that the vaccine comprises a cationic lipid. However, the Office Action alleges that it would have been obvious to combine the '473 patent with Klavinskis et al. or the '409 patent.

Applicants remind the Examiner that it is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant's structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985). Applicants believe that only through the exercise of impermissible hindsight have the cited references been selected and relied upon by the Office. Applicants respectfully submit that there is no teaching or suggestion in the cited art to motivate one of ordinary skill in the art to combine elements of the references to result in the presently claimed invention.

Applicants respectfully reiterate that the selecting an adjuvant for a particular vaccine is per se inventive and not routine experimentation or optimization. The Examiner alleges that the Applicants' arguments that the cited prior art indicates that the successful use of adjuvants depends on many factors, such as the particular antigen it is used in combination with as well as the routes of administration, species of animals used, etc. is not persuasive because all of the references cited by the Applicants were directed to the use of traditional adjuvants, which does not include lipid adjuvants, as is required by the claims and which is allegedly taught in the prior art, such as Klavinskis and the '409 patent. The Examiner alleges that the '409 patent teaches that the lipid complex adjuvant can be used in all mammalian species. Further, the Examiner contends that Applicants have not offered any evidence to indicate that the lipid adjuvants of Klavinskis and the '409 would not work in larger mammals such as bovines or porcines.

In response, Applicants respectfully direct the Examiner to a review article by Sylvia van Drunen Littel-van den Hurk, Shawn L. Babiuk and Lorne A. Babiuk titled "Strategies for improved formulation and delivery of DNA vaccines to veterinary target species" published in Immunological Reviews 2004, Vol. 1999:113-125 ("Babiuk"). The Examiner is respectfully requested to consider and make of record the herewith submitted article, which is also cited on the accompanying Supplemental Information Disclosure Statement and PTO-1449.

Babiuk summarizes the state of the art of DNA immunization of livestock (e.g., bovines and porcines). Babiuk states "[a]lthough the concept of DNA immunization has proven to be extremely successful in inducing immune responses in mice, significant barriers exists to effective induction of immunity in large animals and humans using DNA immunization. Indeed, there is not one DNA vaccine that has been approved for either human or veterinary use" (page 114, bottom of first column of Babiuk). Babiuk also states that "it is clear that DNA immunization of livestock is less effective than that of mice. Whether there are differences in the level of transfection *in vivo* between mice and livestock or whether higher doses of protein are required to stimulate the immune response in livestock is currently unknown" (page 122, top of second column of Babiuk). Thus, induction of an immune response in mice by a DNA vaccine does not necessarily extrapolate to large animals and humans.

Babiuk cites two studies where DMRIE-DOPE resulted in a stronger immune response in ponies and dogs (page 115, bottom first column to top of second column of Babiuk). Interestingly, both of the studies cited by Babiuk list Jean-Christophe Audonnet, an Applicant of the present application, as an author. Babiuk cautions that "[w]ith the exception of these reports, there is a paucity of published information on the use of liposomes for DNA vaccines, specifically in large animals. Therefore, it is difficult to assess the true efficacy of this approach" (page 115, bottom first column to top of second column of Babiuk).

If it would have been obvious to one of ordinary skill in the art, as alleged by the Examiner, to combine the teachings of a bovine or porcine DNA vaccine with the lipid adjuvant of Klavinskis or the '409 patent, then there would have been more than two studies, or at least a study by a laboratory who is not affiliated with an Applicant of the present invention, cited in the Babiuk review article. Furthermore, Babiuk's recitation that "there is a paucity of published information on the use of liposomes for DNA vaccines, specifically in large animals" indicates that it is not accepted by one of skill in the art that such adjuvants are necessarily effective in eliciting an immune response when co-administered with a DNA vaccine in a large animal, such as a bovine or a porcine. Accordingly, Applicants have offered any evidence (e.g., Babiuk) to indicate that the lipid adjuvants of Klavinskis and Wheeler would necessarily not work in larger mammals such as bovines or porcines.

In addition to the herein arguments and herewith literature, and the arguments of record, attention is respectfully directed to MPEP 2143.02 which provides that obviousness requires a reasonable expectation of success. As discussed herein and in the record, and through the literature herewith, there was no reasonable expectation of success of the instant invention prior to the present invention.

The '409 patent relates to an adjuvant composition comprising GAP-DMORIE. However, one of ordinary skill in the art does not recognize that all cationic lipids, such as DMRIE, are necessarily effective adjuvants. The '409 patent admits that cationic lipids were originally studied as cytofectins to enhance delivery of pDNA into cells in-vitro. Such cytofectins may be useful for vaccine applications by enhancing delivery of pDNA into cells responsible for giving rise to the humoral arm of the immune response. Cationic lipids used previously for vaccination shows only low levels of humoral enhancement (col. 2, lines 23-41). GAP-DMORIE, in contrast to the prior art, is useful for enhancing the humoral response (col. 3, lines 27-28). Thus, the '409 patent admits that not all cationic lipids are recognized as effective adjuvants.

Furthermore, according to the '409 patent, vaxfection (GAP-DMORIE/DPyPE at a 1:1 molar ratio) did not have a significant effect on CTL response with either pDNA dose (FIG. 8B) (col. 22, line 7-9). Therefore, there is probably no CTL response with DMRIE.

Applicants respectfully cite U.S. Patent No. 5,719,131 to Harris et al. ("the '131 patent"). The Examiner is respectfully requested to consider and make of record the herein submitted U.S. patent, which is also cited on the accompanying Supplemental Information Disclosure Statement and PTO-1449. According to the '131 patent, although DMRIE has been demonstrated to facilitate (although in many cases only in vitro) the entry of biologically active molecule into cells, it is believed that the uptake efficiencies provided thereby are insufficient to support numerous therapeutic applications (col. 3, lines 43-49). The '131 patent also indicates that DMRIE, a well known transfectant, results in low in vivo expression as shown in FIG. 10 (col 40 lines 46-53).

It is known to one of ordinary skill in the art that a vaccine needs to stimulate both humoral and cellular immunity in order to protect against a viral pathogen (an intracellular microorganism). As indicated by the '409 patent and the '131 patent, DMRIE was known to

induce a low level of expression in-vivo, a weak antibody response and no cytotoxic response. Accordingly, one of skill in the art would not recognize DMRIE as an adjuvant of choice.

Furthermore, attention is respectfully directed to MPEP 2143 which mandates that the fact that references can be combined or modified is insufficient for an obviousness rejection; there must be some desirability in the art to modify reference teachings to arrive at an invention. In the present situation, as discussed herein and in the record, and through the literature herewith, there is no teaching, suggestion, incentive or motivation to modify the cited documents to arrive at the instant invention.

Accordingly, Applicants respectfully request the reconsideration and withdrawal of the double patenting rejections.

II. THE REJECTIONS UNDER 35 U.S.C. §103 ARE OVERCOME

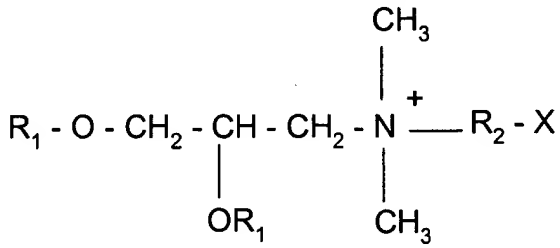
Claims 84-91 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over claims 5-8 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733). Claims 84, 92, 94, 100 and 104 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over claims 5-8 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Li (WO 96/40945). Claims 84, 93, 97, 98 and 104 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over claims 5-8 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Choi et al. (Virology 1998, 250:230-240). Claims 84- 118 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over claims 5-8 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), Baker et al. (US Patent 5,106,733), Li (WO 96/40945) and Choi et al. (Virology 1998, 250:230-240).

Claims 84, 92, 94, 95, 100 and 108 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over claims 5-8 of the '473 patent in view of the '409 patent and further in view of Li (WO 96/40945). Claims 84, 93, 97, 98 and 104 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over claims 5-8 of the '473 patent in view of the '409 patent and further in view of Choi et al. Claims 84-118 were rejected under 35 U.S.C. § 103(a) as allegedly being

obvious over claims 5-8 of the '473 patent in view of the '409 patent and further in view of Xiang et al. (Immunity 1995, 2:129-135), Baker et al. (US Patent No. 5,106,733; 1992), Li (WO 96/40945) and Choi et al. (Virology 1998, 250:230-240).

These rejections are addressed collectively and are respectfully traversed.

The present invention provides a DNA vaccine against a bovine pathogen comprising at least one plasmid that contains and expresses in a bovine host cell a nucleotide sequence encoding an immunogen of the bovine pathogen, wherein the bovine pathogen is BRSV, BVDV-1, BVDV-2 or bPI-3, and a cationic lipid containing a quaternary ammonium salt, of the formula



in which R_1 is a saturated or unsaturated linear aliphatic radical having 12 to 18 carbon atoms, R_2 is an aliphatic radical containing 2 or 3 carbon atoms, and X a hydroxyl or amine group.

The lipid can be DMRIE and the vaccine can further comprise DOPE. The vaccine can also further comprise bovine or porcine GM-CSF, or an expression vector that contains and expresses in a porcine host cell a nucleotide sequence encoding porcine GM-CSF, or an expression vector that contains and expresses in a bovine host cell a nucleotide sequence encoding porcine GM-CSF, wherein this additional expression vector can be a plasmid.

The nucleotide sequence encoding the immunogen can have deleted therefrom a portion encoding a transmembrane domain, and the plasmid can further contain and express in a a nucleotide sequence encoding a heterologous tPA signal sequence, such as a human tPA signal sequence. Even further, the plasmid can further contain a stabilizing intron, such as intron II of a rabbit beta-globin gene.

The Examiner is respectfully directed to the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may

be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." For the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

None of the cited documents teaches or suggests a DNA vaccine that comprises, *inter alia*, a plasmid that expresses DNA encoding an immunogen of a bovine pathogen, wherein the bovine pathogen is BRSV, BVDV-1, BVDV-2 or bPI-3. Neither Klavinskis nor the '409 patent teach or suggest bovine pathogens of BRSV, BVDV-1, BVDV-2 or bPI-3. Xiang, Baker, Li and Choi do not cure the deficiencies of Klavinskis or the '409 patent. Accordingly, in view of the herein arguments and the accompanying reference, reconsideration and withdrawal of the 35 U.S.C. §103 rejection are respectfully requested.

As indicated above, selection of an adjuvant for a particular adjuvant for a particular vaccine is per se inventive and not routine experimentation or optimization. In summary, (a) there is no motivation to combine the cited references (b) the lipid adjuvants of Klavinskis and the '409 patent would not be expected to work in bovines or porcines and (c) one of ordinary skilled in the art would not use a cationic lipid (such as DMRIE) thought to induce a low level of expression, a weak antibody response and no cytotoxic response as an adjuvant.w

In addition to the nonobvious arguments presented above, Applicants also respectfully remind the Examiner to direct his attention to Example 17 on page 65 to 67 of PCT Publication WO 01/5288, which was previously cited on PTO-1449. The data presented in Example 17 of PCT Publication WO 01/5288 presents the neutralizing antibody response of cattle immunized with plasmids expressing gB, gC and gD genes from bovine herpesvirus type-1 (BHV-1) in the presence or absence of DMRIE-DOPE. In the presence of DMRIE-DOPE, the neutralizing response is significantly higher than the neutralizing response in the absence of DMRIE-DOPE. Thus, the above data presents surprisingly superior results when a DNA vaccine is administered to an animal (e.g., cattle) in the presence of a cationic lipid (e.g., DMRIE-DOPE) as compared to administration of the DNA vaccine in the absence of a cationic lipid.

Accordingly, it is respectfully submitted that when one considers all of the teachings in the art, and the mandates of the case law and the MPEP, it is clear that the rejections cannot stand.

Therefore, the cited documents fail to teach or suggest the instant invention. Applicants reiterate that there is no motivation to combine the '473 patent with Klavinskis or the '409 patent. Xiang, Baker, Li and Choi do not cure the deficiencies of the '473 patent or the '409 patent. Accordingly, in view of the herein arguments and the accompanying references, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are respectfully requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested; and, the Office Action is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,
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